Amendments to the Specification:

Replace the paragraph beginning at page 7, line 22 with the following amended paragraph:

The invention features a nucleic acid molecule which is at least 45% (or 55%, 65%, 75%, 85%, 95%, or 98%) identical to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the nucleotide sequence of the cDNA insert of the plasmid deposited with the ATCC as Accession Number _____ (the "cDNA of ATCC _____"),~~ or a complement thereof.

Replace the paragraph beginning at page 7, line 27 with the following amended paragraph:

The invention features a nucleic acid molecule which includes a fragment of at least 150 (300, 325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, 1300, 1600, 1900, 2100, 2400, 2700, 3000, or 3100) nucleotides of the nucleotide sequence shown in SEQ ID NO:1, or SEQ ID NO:3, ~~or the nucleotide sequence of the cDNA ATCC _____~~, or a complement thereof.

Replace the paragraph beginning at page 7, line 32 with the following amended paragraph:

In an embodiment, a CARD-12 nucleic acid molecule has the nucleotide sequence shown in SEQ ID NO:1, or SEQ ID NO:3~~, or the nucleotide sequence of the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 8, line 1 with the following amended paragraph:

Also within the invention is a nucleic acid molecule which encodes a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:2 ~~or the polypeptide encoded by the cDNA of ATCC Accession Number _____~~.

Replace the paragraph beginning at page 8, line 4 with the following amended paragraph:

The invention includes a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein

the nucleic acid molecule hybridizes to a nucleic acid molecule consisting of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the cDNA of ATCC~~ under stringent conditions.

Replace the paragraph beginning at page 9, line 1 with the following amended paragraph:

Also within the invention are: an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 65%, preferably 75%, 85%, or 95% identical to SEQ ID NO:3~~or the cDNA of ATCC _____~~; an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 85%, 95%, or 98% identical to the P-loop domain encoding portion of SEQ ID NO:3; an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical the CARD domain encoding portion of SEQ ID NO:3; an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical the NAIP homology encoding portion of SEQ ID NO:3; an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical the nucleotide binding site domain encoding portion of SEQ ID NO:3; an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical to the LRR domain encoding portion of SEQ ID NO:3 or one or more leucine rich repeat encoding portions of SEQ ID NO:3; and an isolated CARD-12 protein which is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:3 ~~or the non-coding strand of the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 9, line 23 with the following amended paragraph:

Another embodiment of the invention features CARD-12 nucleic acid molecules which specifically detect CARD-12 nucleic acid molecules, relative to nucleic acid molecules encoding other members of the CARD superfamily and/or members of the NBS/LRR superfamily. For example, in one embodiment, a CARD-12 nucleic acid molecule hybridizes under stringent

conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, ~~or the cDNA of ATCC _____~~, or a complement thereof. In another embodiment, the CARD-12 nucleic acid molecule is at least 300 (350, 400, 450, 500, 550, 600, 650, 700, 800, 900, 1000, 1300, 1600, 1900, 2100, 2400, 2700, 3000, or 3100) nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____~~, or a complement thereof. In another embodiment, an isolated CARD-12 nucleic acid molecule comprises the CARD domain encoding portion of SEQ ID NO:3, or a complement thereof. In yet another embodiment, the invention provides an isolated nucleic acid molecule which is antisense to the coding strand of a CARD-12 nucleic acid.

Replace the paragraph beginning at page 15, line 9 with the following amended paragraph:

The domain alignments depicted in Figures 5A-5E were identified by homology searching using consensus domains derived from hidden Markov models (HMMs). HMMs can be used to perform multiple sequence alignment and very sensitive database searching, using statistical descriptions of a domain's consensus sequence. ~~For more information on HMM searches, see, e.g., http://hmmer.wustl.edu/.~~ In the alignments of Figures 5A-5E a single letter amino acid designation at a position on the line between the CARD-12 sequence and the HMM-generated consensus domain sequence indicates an exact match between the two. A "+" in this middle line indicates a conservative substitution at the particular residue of CARD-12. Amino acid residues located in the domains identified by the HMM search may be important for the appropriate functioning of the CARD-12 protein. For this reason, amino acid substitutions with respect to the sequence of SEQ ID NO:2 that are outside of the domains homologous to HMM consensus domains may be less detrimental to the activity of the CARD-12 protein.

Delete the paragraph beginning at page 16, line 4 that starts with " A plasmid containing...".

Replace the paragraph beginning at page 19, line 1 with the following amended paragraph:

A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____~~, or a complement of any of these nucleotide sequences, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequences of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, the cDNA of ATCC _____~~, as a hybridization probe, CARD-12 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., eds., Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Replace the paragraph beginning at page 19, line 17 with the following amended paragraph:

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____~~, or a portion thereof. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Replace the paragraph beginning at page 19, line 23 with the following amended paragraph:

Moreover, the nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding CARD-12, for example, a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of CARD-12. The nucleotide sequence determined from the cloning of the human CARD-12 gene allows for the generation of probes and primers designed for use in identifying and/or cloning CARD-12 homologues in other cell types, e.g., from other tissues, as well as CARD-12 homologues and orthologs from other mammals. The probe/primer typically comprises substantially purified

oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, the cDNA of ATCC _____~~, or of a naturally occurring mutant of one of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 20, line 10 with the following amended paragraph:

A nucleic acid fragment encoding a "biologically active portion" of CARD-12 can be prepared by isolating a portion of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the cDNA of ATCC _____~~, which encodes a polypeptide having a CARD-12 biological activity, expressing the encoded portion of CARD-12 protein (e.g., by recombinant expression in vitro) and assessing the activity of the encoded portion of CARD-12. For example, a nucleic acid fragment encoding a biologically active portion of CARD-12 includes a CARD domain, e.g., amino acids 1-88 of SEQ ID NO:2.

Replace the paragraph beginning at page 20, line 17 with the following amended paragraph:

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, and the cDNA of ATCC _____~~, due to degeneracy of the genetic code and thus encode the same CARD-12 protein as that encoded by the nucleotide sequence shown in SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 20, line 22 with the following amended paragraph:

In addition to the CARD-12 nucleotide sequence shown in SEQ ID NO:1~~,~~ and SEQ ID NO:3~~, and the cDNA of ATCC _____~~, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of CARD-12

may exist within a population (e.g., the human population). Such genetic polymorphism in the CARD-12 gene may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a CARD-12 protein, preferably a mammalian CARD-12 protein. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the CARD-12 gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in CARD-12 that are the result of natural allelic variation and that do not alter the functional activity of CARD-12 are intended to be within the scope of the invention. Thus, e.g., 1%, 2%, 3%, 4%, or 5% of the amino acids in CARD-12 (e.g., 1, 2, 3, 4, 5, 6, 8, 10, 15, or 20 amino acids) are replaced by another amino acid, preferably by conservative substitution.

Replace the paragraph beginning at page 21, line 4 with the following amended paragraph:

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 150 (300, 325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, 1300, 1600, 1900, 2100, 2400, 2700, 3000, or 3100) nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 21, line 23 with the following amended paragraph:

In addition to naturally-occurring allelic variants of the CARD-12 sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequence of SEQ ID NO:1~~,~~ or SEQ ID NO:3, ~~or the cDNA of ATCC _____~~, thereby leading to changes in the amino acid sequence of the encoded protein without altering the functional ability of the protein. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of CARD-12 protein without altering the biological activity, whereas an "essential" amino acid

residue is required for biological activity. For example, amino acid residues that are conserved among the CARD-12, proteins of various species are predicted to be particularly unamenable to alteration.

Replace the paragraph beginning at page 22, line 5 with the following amended paragraph:

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding CARD-12 proteins that contain changes in amino acid residues that are not essential for activity. Such CARD-12 proteins differ in amino acid sequence from SEQ ID NO:2, and yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 45% identical, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:2. An isolated nucleic acid molecule encoding a CARD-12 protein having a sequence which differs from that of SEQ ID NO:1, or SEQ ID NO:3~~, or cDNA of ATCC _____~~, can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of CARD-12 (SEQ ID NO:1, or SEQ ID NO:3~~, the cDNA of ATCC _____~~) such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. Thus, for example, 1%, 2%, 3%, 5%, or 10% of the amino acids can be replaced by conservative substitution. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in CARD-12 is preferably replaced with another amino acid residue from the same side

chain family. Alternatively, mutations can be introduced randomly along all or part of a CARD-12 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for CARD-12 biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

Replace the paragraph beginning at page 28, line 24 with the following amended paragraph:

The determination of percent homology between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) Proc. Nat'l Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul (1993) Proc. Nat'l Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences similar or homologous to CARD-12 nucleic acid molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997) Nucleic Acids Res. 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. ~~See http://www.ncbi.nlm.nih.gov.~~ Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. When utilizing the ALIGN program for comparing nucleic acid sequences, a gap length penalty of 12, and a gap penalty of 4 can be used.

Replace the paragraph beginning at page 48, line 15 with the following amended paragraph:

A transgenic animal of the invention can be created by introducing CARD-12-encoding nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The CARD-12 cDNA sequence, e.g., that of SEQ ID NO:1, or SEQ ID NO:3 ~~or the cDNA of ATCC ____~~ can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homolog or ortholog of the human CARD-12 gene, such as a mouse CARD-12 gene, can be isolated based on hybridization to the human CARD-12 cDNA and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the CARD-12 transgene to direct expression of CARD-12 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the CARD-12 transgene in its genome and/or expression of CARD-12 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding CARD-12 can further be bred to other transgenic animals carrying other transgenes.

Replace the paragraph beginning at page 56, line 5 with the following amended paragraph:

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, i.e., candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) which bind to CARD-12 proteins or biologically active portions thereof or have a stimulatory or inhibitory effect on, for example,

CARD-12 expression or CARD-12 activity. An example of a biologically active portion of human CARD-12 is amino acids 1-88 ~~139-227~~ encoding a CARD domain.